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Predictors of Severe Diabetic Gastroparesis in Patients with 2 Type Diabetes Mellitus

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Abstract Diabetic gastroparesis is a heterogeneity of gastrointestinal symptoms ranging from asymptomatic manifestations up to mimicking by other nosological units which hampers to make a timely diagnosis. **Objective.** To identify the predictors of severe diabetic gastroparesis (DG) in patients with 2 type diabetes mellitus (DM2). **Materials and methods.** In the period from September 2020 to December 2021, 1026 patients with diabetes mellitus complicated by gastroparesis were treated. Taking into account the exclusion criteria (type 1 diabetes mellitus - 97 patients, thyroid-stimulating hormone level <0,1 and >4,5 μIU/ml - 23 patients, patients with mild DG according to the sum of the PAGI-SYM questionnaire scale ≤11-501 patients) 405 patients were included in this study. Data were collected including the definition of the clinical manifestation of gastropathy clarified by means of PAGI-SYM questionnaire. Univariate and multivariate analyzes were used to evaluate significant prognostic predictors of severe DG. **Results.** The mean age of the patients was 59,35±6,42 years with the duration of the underlying disease 12,39±4,84 years. The mean value of glycosylated hemoglobin was 10,12±1,76% [6,6–17,1%]. The average body mass index was 30,33±3,55 kg/m^2. In multivariate analyse, vomiting (OR: 11,37; 95% CI: 4,36-29,63; p<0,001), the inability to master the usual portion of meal (OR: 6,69; 95% CI: 1,63-27,4; p<0,001), chest discomfort when lying down at night (OR: 2,63; 95% CI: 1,4-4,9; p<0,001), bitter or sour taste in the mouth (OR: 5,95; 95% CI: 2,02-17,52; p<0,001) were predictors of severe DG. It was also found that there is no correlation between the 5-, 10-, 15-year duration of the disease and severe degree of DG (p=0,833, p=0,623, p=0,553, respectively) which indicates the progression of gastroparesis regardless of the duration of DM2. **Conclusions.** Vomiting, the inability to master the usual portion of meal, chest discomfort when lying down at night, bitter or sour taste in the mouth are strongest predictors of severe DG regardless of the duration of DM2. Early diagnosis of DG with determining the severity of this complication can help to conduct timely conservative stage-related therapy in order to normalize the motor-evacuation function of the stomach.

Keywords Diabetic gastroparesis, 2 type diabetes mellitus, PAGI-SYM questionnaire

1. Introduction

As known, DM2 poses a threat to the development of microangiopathy (neuropathy, nephropathy, retinopathy) and thus is considered as a consequential cause of deterioration in the life quality and reduction in life expectancy of patients [4,6]. Diabetic autonomic neuropathy is often not diagnosed and treated inadequately which itself can lead to cardiovascular autonomic neuropathy and gastrointestinal motility disorder - DG [8,12]. Unfortunately, clinicians pay insufficient attention to this chronic complication of DM2 because of its course under the "masks" of other nosological units that contributes to the difficulties of early diagnosis. The true prevalence of motor-evacuation dysfunction in patients with DM2 is probably underestimated. Kassander wrote in 1958 that "this syndrome is much more often 'missed' than diagnosed" [5]. To date, there are scarce data on the epidemiology of DG in patients with DM2, although this complication is not a rare occurrence and ranges from 25% to 70% of cases in the DM2 population [3,7,13].

It has been suggested that the motor-evacuation dysfunction of the stomach does not affect the life expectancy of patients with DM2 [9]. Although DG in patients with DM2 is one of the reasons for the difficulty in achieving target glycaemic control and a decrease in the life quality of patients [10]. A slowdown in the evacuation of food from the stomach can contribute to postprandial hypoglycaemia followed by hyperglycaemia, which affects the development/progression of late complications of DM2 [12]. An increase in the frequency of hypoglycaemia in motor-evacuation dysfunction of the stomach in patients with DM2 is associated with a discrepancy between the peak action of prandial insulin and the rate of absorption of carbohydrates in the small intestine [1].

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DG impairs also the bioavailability of oral medications due to the possible reflux of gastric contents into the respiratory tract that affects the treatment of comorbidities and increases the risk of complications during surgical interventions requiring anaesthesia [10].

Currently, there are no clear indications for instrumental research methods in order to screen disorders of the motor-evacuation function of the stomach in patients with DM2. In the process of collecting complaints and analysing the history of the disease (duration of DM2, dynamics of glycemia, lability of the course), it can be assumed that the patient has initial symptoms of DG. For a more accurate diagnosis of the asymptomatic course of this complication, Revicki D.A. and co-authors developed a specialized questionnaire which was tested in several multicentre studies and today has a high evidence of base [13]. Moreover, in the highly developed countries of the world, general practitioners and doctors of subspecialties use widely these questionnaires to assess the severity index of gastroparesis symptoms in patients with DM2 in daily medical practice. This diagnostic method also allows the patient to independently assess symptoms that have occur within two weeks of disease onset [2,14].

The relationship between various gastrointestinal symptoms and the degree of motor-evacuation dysfunction, measures of glycaemic control which could serve as clinical markers or predictors of severe DG in patients with DM2 [11], is not well understood or is ambiguous.

2. Materials and Methods

The sample size was 1026 patients with diabetes mellitus complicated by gastroparesis. This prospective observational study included 405 patients with DM2 aged 18 to 75 years who were hospitalized at the Republican specialized scientific and practical medical center of endocrinology from September 2020 to December 2021. Exclusion criteria were type 1 diabetes mellitus - 97 patients, thyroid-stimulating hormone level <0,1 and >4,5 μIU/ml (23 patients), mild DG according to the sum of the PAGI-SYM questionnaire scale ≤11 (501 patients), whereas inclusion criteria - DM2, PAGI-SYM>20; thyroid-stimulating hormone 0,1-4,5 μIU/ml. The informed consent from patients was obtained.

Data collection according to the questionnaire and scale measurement technique. The degree of DG was assessed using the PAGI-SYM questionnaire scale. The questionnaire consists of 20 questions, combining 6 subscales: heartburn/regurgitation (7 questions), nausea / vomiting (3 questions), feeling of postprandial fullness (postprandial distress syndrome)/early feeling of fullness (4 questions), meteorism/bloating (2 questions), pain in the upper abdomen (2 questions), pain in the lower abdomen (2 questions). The PAGI-SYM questionnaire allows the patient to assess subjective signs of symptom severity over a two-week period by assessing symptoms on a 5-point scale, where 0 means no symptoms, 1 is a minor symptom, 2 is a mild symptom, 3 is a severe symptom, 5 is more severe symptom. The sum of all points determines the degree of severity:

mild degree (1–11 points);

moderate degree (12–22 points);

severe degree (23–33 points).

Assessment of the symptoms of DG according to the PAGI-SYM questionnaire is presented in Table 1.

Table 1. PAGI-SYM questionnaire

№	***Symptoms***					
1	Nausea	1	2	3	4	5
2	Gagging	1	2	3	4	5
3	Vomiting	1	2	3	4	5
4	Heaviness in the stomach	1	2	3	4	5
5	Inability to muster the usual amount of food	1	2	3	4	5
6	Feeling overly full after eating	1	2	3	4	5
7	Loss of appetite	1	2	3	4	5
8	Bloating	1	2	3	4	5
9	Stomach or belly is visually larger	1	2	3	4	5
10	Pain in the upper abdomen (above the navel)	1	2	3	4	5
11	Discomfort in the upper abdomen (above the navel)	1	2	3	4	5
12	Pain in the lower abdomen (below the navel)	1	2	3	4	5
13	Discomfort in the lower abdomen (below the navel)	1	2	3	4	5
14	Heartburn during the day	1	2	3	4	5
15	Heartburn in the supine position	1	2	3	4	5
16	Chest discomfort during the day	1	2	3	4	5
17	Chest discomfort at night (during sleep)	1	2	3	4	5
18	Regurgitation or reflux throughout the day	1	2	3	4	5
19	Regurgitation in the supine position	1	2	3	4	5
20	**Bitter or sour taste in the mouth**	**1**	**2**	**3**	**4**	**5**

3. Results and Discussion

To eliminate systematic errors, the subjects were stratified into two groups according to gender characteristics: the first group - 199 men; the second group - 206 women.

The mean age of the patients was 59,35±6,42 years. Clinical characteristics of patients are shown in Table. 2.

According to the obtained data, male and female patients were identical. Among all complications, diabetic polyneuropathy occurred in the majority of 97,9% and 99,0% of cases in male and female patients, respectively. The next most common complication was diabetic encephalopathy in 83%-84% of cases, other complications such as diabetic nephropathy, retinopathy, diabetic foot syndrome occurred in 4,4%-47% of cases (Table 2).

In terms of the presence of concomitant diseases, men and women were also identical, except for coronary heart disease, obesity, which showed the presence of a direct relationship of these diseases with the female sex (p=0,001).

Table 2. Clinical characteristics of patients, n (%)

Parameters	DM2	Male	Female	*P*
Age, years	59,35±6,42	58,23±9,31	59,43±8,44	**0,24**
Duration DM2, years	12,39±4,84	12,60±5,90	12,19±5,98	**0,48**
HbA1c, %	10,12±1,76	9,65±1,64	9,78±2,23	**0,44**
Body mass index, kg/m^2	30,33±3,55	29,27±4,13	31,37±5,04	**0,03**
Complications of DM2				
Diabetic polyneuropathy	399 (98,5)	195 (97,9)	204 (99,0)	**0,39**
Diabetic encephalopathy	339 (83,7)	166 (83,4)	173 (83,9)	**0,87**
Diabetic nephropathy	186 (45,9)	94 (47,2)	92 (44,6)	**0,60**
Nonprolipherative retinopathy	163 (40,2)	81 (40,7)	82 (39,8)	**0,85**
Preprolipherative retinopathy	59 (14,5)	24 (12,0)	35 (16,9)	**0,17**
Diabetic foot syndrome	40 (9,9)	31 (15,5)	9 (4,4)	**0,00**
Prolipherative retinopathy	**23 (5,6)**	**14 (7,0)**	**9 (4,4)**	**0,25**

The degree of carbohydrate metabolism compensation was assessed according to standards [11]. Clinical examination of patients consisted of a detailed analysis of anamnestic data, PAGI-SYM questionnaire and assessment of physical status, a standard set of laboratory parameters, clinical and biochemical blood tests.

According to the degree of compensation of carbohydrate metabolism, a compensated form of the disease was detected in 162 (40%) patients, whereas sub- and decompensated forms of DM2 were established in the majority of 243 (60%) patients.

3.1. Data According to Study of the PAGY-SYM Questionnaire

The assessment of the scales of the PAGI-SYM questionnaire showed the presence of specific complaints including bloating, heaviness in the stomach, a feeling of fullness after eating, discomfort in the upper abdomen (above the navel), heartburn in a standing position, inability to master the usual amount of food, loss of appetite, bitter or sour taste in the mouth, discomfort in the chest during the day, discomfort in the lower abdomen (below the navel) in 93-99% of cases. According to the severity of symptoms, pain in the upper abdomen (above the navel), nausea, visually larger abdomen were identified in 80-87% of cases.

All other least common symptoms of DG in 23-67% of cases were the following: pain in the lower abdomen (below the navel), food regurgitation when standing, discomfort in the chest at night, heartburn when lying down, feeling full of food/gagging (without vomit), food regurgitation in the supine position, vomiting. According to the PAGI-SYM questionnaire, the above symptoms of DG occurred equally, and the mean PAGI-SYM score did not differ between men and women.

Moreover, the distribution of severe and moderate degree of DG among men and women with DM2 was identical (163 vs 180; p=0,215 and 36 vs 26; p=0,328, respectively).

According to the results of the correlation analysis, gastrointestinal symptoms and C-reactive protein value had a direct correlation with severe DG, which were included in univariate and multivariate regression analyses. The identified predictors by means of regression analysis are presented in Table 3.

According to the data obtained, in patients with DM2, symptoms such as vomiting - OR 11,37 (4,36-29,63; 95% CI), the inability to master the usual portion of food - OR 6,69 (1,63-27,4; 95% CI), chest discomfort in the supine position - OR 2,63 (1,4-4,9; 95% CI), bitter or sour taste in the mouth - OR 5,95 (2,02-17,52; 95% CI) as predictors may indicate a deterioration of the motor-evacuation function of the stomach in the absence of primary diseases of the gastrointestinal tract.

The influence of the duration of DM2 on the occurrence of DG was assessed, and it was found that there is no correlation between the 5-, 10-, 15-year duration of the disease and the moderate and severe degrees of DG (p=0,833; p=0,623; p=0,553, respectively) which indicates the progression of this complication regardless of the duration of DM2.

The use of the PAGI-SYM questionnaire which consists of 20 questions, contributes to a comprehensive study of the progression of DG from the first days of diagnosing DM2. At the same time, the PAGI-SYM questionnaire makes it possible to determine the degree of motor-evacuation dysfunction of the stomach in such category of patients.

According to the results of our study, 4 gastrointestinal symptoms (vomiting, inability to master the usual portion of food, discomfort in the chest in the supine position (at night), bitter or sour taste in the mouth) were identified as predictors of the development DG in DM2 patients. At the same time, the definition of the above 4 predictors can facilitate the detection of DG in the early period of the onset of this complication.

Table 3. Logistic regression to determine predictors of gastric motor-evacuation dysfunction in diabetic gastropathy

Parameters	Univariate OR (95% CI)	*P*	Multivariate OR (95% CI)	*P*
HbA1C, %	0,95 (0,84-1,09)	0,495	-	
C-reactive protein	1,00 (0,92-1,08)	0,984	-	
C-reactive protein associated with CVD risks, %	1,24 (0,85-1,81)	0,264	-	
Nausea	1,32 (0,6-2,91)	0,489	-	
Gagging	9,94 (3,16-31,22)	**<0,001**	11,37 (4,36-29,63)	**<0,001**
Vomiting	1,64 (0,26-10,43)	0,602	-	
Inability to muster the usual amount of food	9,43 (1,95-45,6)	**0,005**	6,69 (1,63-27,4)	**0,008**
Stomach or belly is visually larger	1,55 (0,67-3,6)	0,309	-	
Pain in the upper abdomen (above the navel)	1,85 (0,68-4,99)	0,225	-	
Pain in the lower abdomen (above the navel)	1,12 0,45-2,72)	0,810	-	
Discomfort in the upper abdomen (above the navel)	1,01 (0,58-1,62)	**0,028**	0,54 (0,22-1,3)	**0,072**
Heartburn in the supine position	1,49 (0,7-3,15)	0,3	-	
Chest discomfort at night (during sleep)	2,11 (1,00-4,46)	**0,049**	2,63 (1,4-4,9)	**0,002**
Regurgitation or reflux throughout the day	1,74 (0,82-3,72)	0,150	-	
Regurgitation in the supine position	1,75 (0,57-5,38)	0,331	-	
Bitter or sour taste in the mouth	3,97 (1,15-13,62)	**0,029**	5,95 (2,02-17,52)	**0,001**

The absence of a correlation between DG-associated symptoms and the duration of disease indicates the occurrence of DG in any DM2 form (compensatory, sub-or decompensatory).

Limitations. Although a relatively large series of patients with DM2 complicated with DG were retrospectively analysed, the sample size was small, and some observations might have limited statistical power. The retrospective data were collected from medical reports of patients, and the patient surveys were provided by different physicians. In addition, the study cannot provide an explanation for the different outcomes, which are likely to be multifactorial, including potential genetic and physiologic variances and possible differences in health care systems.

4. Conclusions

Along with well-known complications such as diabetic polyneuropathy, retinopathy, nephropathy, DG is also the most common specific complication of DM2. Considering that DG can occur in any form (compensatory, sub-or decompensatory form) of DM2, clinicians should also pay attention and carry out timely complex treatment to eliminate this kind of complication, based on the identification of DG predictors (vomiting, inability to master the usual portion of food, discomfort in the chest in the supine position (at night), bitter or sour taste in the mouth).

In conclusion, early diagnosis of DG, determining the severity of this complication, can help to conduct timely conservative stage-related therapy in order to normalize the motor-evacuation function of the stomach. Future studies should be focused on analysing the significance of the impact of conservative treatment of DG on glycaemic and lipid profile control and assessing the importance of including this therapy in the complex treatment of DM2.

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